A1 cont size of between .1 and 2 microns.---

REMARKS

Claims 1-18 are pending in this application. Claims 1, 5, 7-9, 11-12, 14 and 16-18 are rejected under 35 U.S.C. §102(b) and claims 1-18 are rejected under 35 U.S.C. §103. Applicants have canceled Claims 1-18 and replaced them with new claims 19-48, in order to more definitely point out and distinctly claim the subject of the application. The subject matter of the new claims is fully supported in the specification and claims as originally filed. For reasons set forth below, Applicants request that the rejections be withdrawn and the pending claims allowed to issue.

1. The Claims Are Not Anticipated

Claims 1, 5, 7-9, 11-12 and 14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gilbert et. al (1993, Transplantation 56: 974-7; "Gilbert"). Claims 16-18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Adjei et al. (U.S. Patent 5,635,161: "Adjei"). These rejections are in error and should be withdrawn for the reasons set forth below.

Anticipation requires that all the elements and limitations of the claims be found within a single prior art references. There must be no difference between the claimed invention and the reference disclosures, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 927 F.2d 1565, 18 U.S.P.Q.2d 1001,

18 U.S.P.Q.2d 1896 (Fed. Cir. 1991). Further, the use of the claim phrase "consisting essentially of" excludes ingredients that would materially effect the basic and novel characteristics of the claimed compositions. *Atlas Powder Co. v E.I. du Pont de Nemours & Co.*, 750 F2d 1569, 224 U.S.P.Q. 409 (Fed. Cir. 1984); Manual of Patent Examining Procedure §2111.03 (6th ed. 1997).

In the present instance, the claims as amended encompass aerosolized compositions "consisting essentially of" : (i) cyclosporine and a propellant; (ii) cyclosporine, a dry powder and a propellant; or (iii) cyclosporine, an organic solvent and a propellant, and the use of such compositions for prevention of graft rejection, pulmonary inflamation and/or inhibition of the immune response associated with T-cell mediated immune disorders using such compositions.

In contrast Gilbert discloses the generation of small particle aerosol liposomes containing cyclosporine and the use of such liposomes as an immunosuppressive agent to treat lung disease. Additionally, Adjei merely discloses drug formulations for aerosol delivery comprising a vegetable oil in combination with a medicament and a non-chlorofluorocarbon propellant. Adjei teaches that one such medicament may be cyclosporine.

With regard to Adjei, Applicants assert that the claims as amended fail to encompass compositions containing cyclosporine and a vegetable oil as described by Adjei. In addition, the claims as amended fail to encompass compositions comprising small particle aerosol liposomes containing cyclosporine and the use of such liposomes as an immunosuppressive agent to treat lung disease as described by Gilbert.

Moreover, the encapsulation of cyclosporine into liposomes would materially alter the characteristics of Applicant's claimed compositions and methods. Liposome encapsulated cyclosporine would have altered pharmacokinetic properties as compared to non-encapsulated formulations of cyclosporine. For example, because liposomes resemble cell membranes in their structure and composition, the delivery of a liposome encapsulated drug into a cell would be expected to occur as a fusion event between the cell membrane and the liposome membrane resulting in the transfer of the drug into the cell. (see Exhibit A, Lasic, 1998, *TIBTECH*, 16:307-321; p.313-314). Clearly, compositions such as Applicants, in which the cyclosporine is non-encapsulated, could not enter the cell via a membrane fusion event.

Therefore, given the differences between the cited references and the present invention, the references cannot anticipate the present invention and the rejection under 35 U.S.C. § 102(b) should be withdrawn.

2. THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 1-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Adjei and Waldrep et al. (U.S. Patent 5,956,378; "Waldrep"), in view of Gilbert, Knight et al. (U.S. Patent 5,049,388) and Applicant's admission on the record. According to the Examiner Adjei, Waldrep, Gilbert, Knight and Applicant admit on the record that the claimed compounds are old and well known in combination with various pharmaceutical carriers and excipients in a dosage

form. According to the Examiner, these medicaments are thought as useful for treating graft rejection, inflammation and those conditions claimed and disclosed by Applicant.

A finding of obviousness under §103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the difference between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere,* 383 U.S.1, (1996). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. In *re: O'Farrell,* 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Circ. 1988). In addition, "one way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of unexpected results", *In re Soni*, 54 F. 3d 746, 34 U.S.P.Q. 2d 1684 (Fed. Cir. 1995).

In the present instance, the relevant inquiry is whether any of the cited references suggest compositions of non-encapsulated aerosolized cyclosporine and their use for prevention of graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders.

A review of the Waldrep, Gilbert and Knight references reveals that each of the references only disclose compositions comprising liposomal encapsulated cyclosporine. Applicants assert that one of ordinary skill in the art would recognize that liposomal formulations containing cyclosporine would have altered pharmacokinetic properties, such as biodistribution,

clearance rates, and toxicity as compared to non-encapsulated formulations of cyclosporine. In this regard, the Examiner's attention is invited to column 2, lines 5-7, of the Knight reference cited by the Examiner which states the following: " in laboratory animals the use of liposomes actually reduced toxic effects observed with the drug alone." However, Applicants have demonstrated, unexpectedly, that doses of non-encapsulated cyclosporine as high as 300 mg per day are tolerated by the treated patient as demonstrated by the working examples presented in the specification (Example 6, p.22-28 of the specification). Indeed, the disclosure of Knight would seem to teach away from Applicants' claimed invention, further indicia of non-obviousness. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F. 2d 443, 230 U.S.P.Q. 416 (Fed. Cir. 1986)

Thus, the mere disclosure of liposomal formulations of cyclosporine would fail to suggest the claimed methods and compositions of the invention, *i.e.*, non-encapsulated formulations of cyclosporine, nor provide any expectation that the claimed methods utilizing such compositions could successfully be practiced.

In addition, although Adjei discloses compositions of non-encapsulated cyclosporine, Adjei fails to disclose or suggest that such non-encapsulated compositions could be successfully used to prevent graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders using such compositions. Further, this deficiency in the teaching of Adjei is not remedied by any of the additionally cited references.

In summary, Adjei and Waldrep, in combination with Gilbert and Knight, fail to suggest the compositions of the claimed invention or provide a reasonable expectation of success in the use of such compositions for prevention of graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders. Applicants respectfully request, therefore, that the rejections under 35 U.S.C. §103 be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Applicant believes that the invention described and defined by the claims is patentable. Withdrawal of all rejections and consideration of the new claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

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Enclosures